REMARKS

Claims 1, 2, 13 to 35 and 41 are under consideration. By this response, claims 50 to 55 and 38 to 40 have been cancelled herein without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit or priority of the subject application. Claims 64 to 84, which are in the elected invention, have been added. Accordingly, upon entry of this Response, claims 1, 2, 13 to 35, 41 and 64 to 84 are under consideration.

Regarding the Amendments

The amendments to the claims are supported throughout the specification or were made to address an informality. In particular, the amendments to claims 1 to recite "and secreted in an active form" is supported, for example, at page 9, third paragraph. The amendment to delete reference to "Factor IX" were made in view of new claims 64 to 84, which substantially parallel claims 1, 2, 13 to 35 and 41, except recite "Factor IX." The amendment to claim 41 was made to correct a typographical error in the spelling of "claim." Thus, as the amendments are supported throughout the specification or were made to address an informality, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claims

New claims 64 to 84 are supported throughout the specification. In particular, claims 64 to 84 substantially parallel claims 1, 2, 15 to 18 and 21 to 35, and are therefore supported, for example, by originally filed claims 1 to 9, 15 to 17, 21 to 35 and 41 and as set forth in the record for the amendments to any of claims 1, 2, 15 to 18 and 21 to 35. Thus, as claims 64 to 84 are supported throughout the specification, no new matter has been added and entry thereof is respectfully requested.

Regarding the Objection to Claim 34

Applicants respectfully request that the objection be withdrawn. In this regard, claim 34 depends from claim 33, which in turn is directed to a polypeptide encoded by the recombinant polynucleotide of claim 1. Claims 33 and 34 therefore ultimately depend from claim 1 of the elected invention. Because both claims 33 and 34 ultimately depend from claim 1, if claim 1 is

allowable claims 33 and 34 would also be allowable. Accordingly, Applicants respectfully request rejoinder of these claims with the elected invention. Analogously, new claim 81 depends from new claim 64 of the elected invention and therefore would also be allowable if claim 64 is allowable. Examination of claims 33, 34 and 81 would not be an undue burden. In this regard, a reference applied as art against claims 1, 2, 13 to 35, 41, 64 to 80 and 82 to 84 may also be applied by the Examiner against claims 33, 34 and 81. Thus, as a search of the art would identify art applicable to claims 1, 2, 13 to 35, 41, 64 to 80 and 82 to 84, as well as claims 33, 34 and 81 examination of these claims would not be an undue burden on the Patent Office. In view of the foregoing, Applicants respectfully request rejoinder of claims 33 and 34, and new claim 81 with the elected invention and that the objection to claim 34 be withdrawn.

I. REJECTIONS UNDER 35 U.S.C. §103(a)

The rejection of claims 1, 2, 13 to 25, 29, 30, 32, 34, 35 and 41 under 35 U.S.C. §103(a), as allegedly unpatentable over Wolf *et al.* (U.S. Patent No. 5,795,863) in view of Nicolaisen *et al.* (U.S. Patent No. 5,580,560) is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 3-5. Namely, Wolf *et al.* allegedly describe " a slow release form of Factor X....wherein said proteolytic cleavage site has the sequence RKRRKR" but "does not specifically teach Factor VII or Factor IX having the proteolytic cleavage site." Allegedly Nicolaisen *et al.* describe "that the cDNA coding for Factor VII has been characterized," and that "one of ordinary skill in the art would have been motivated to combine the teaching to produce a slow release form of Factor VII."

Claims 1, 2, 13 to 25, 29, 30, 32, 34, 35 and 41 would not have been obvious in view Wolf *et al.* (U.S. Patent No. 5,795,863) alone, or in combination with Nicolaisen *et al.* (U.S. Patent No. 5,580,560) at the time of the invention. Solely in order to further prosecution of the application, the amended and new claims recite "secreted in an active form." The rejection will therefore be addressed as if applied to the amended and new claims upon entry of this Response.

In order to establish obviousness under 35 U.S.C. §103(a), there must have been a suggestion or motivation to modify the reference; a reasonable expectation of success of producing the claimed invention; and the reference must teach or suggest each and every claim limitation. Both the teaching or suggestion to make the claimed combination *and* the reasonable expectation of success *must both be found in the prior art, not in Applicants' disclosure.* See,

e.g., *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) and *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988), *Emphasis added.* "The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification." *In re Gordon,* 733 F.2d 900, 902 (Fed. Cir. 1984); *See, also, In re Mills*, 916 F.2d 680 (Fed. Cir. 1990).

As a first issue, Wolf *et al.* is directed to modified forms of Factor X that are inactive (see, for example, column 3, lines 39-47 and 56-59; and column 16, Example 10). The purpose of such modified Factor X is to treat thrombus formation i.e., to inhibit clotting (see, for example, column 3, lines 12-16 and 20-26; and column 7, lines 61-64). In contrast, the claims are directed to recombinant polynucleotides that encode modified forms of Factor VII or Factor IX that are cleaved at the cleavage site when expressed in an animal cell and secreted in an active form i.e., promote clotting. Thus, as the purpose of the Wolf *et al.* patent is to modify Factor X to inhibit clotting whereas the claimed polynucleotides encode modified forms of Factor VII or Factor IX that can promote clotting, Wolf *et al.* is for a purpose opposite to that of the claimed polynucleotides.

As a second issue, as recognized by the Patent Office Nicolaisen *et al.* modify Factor VII in order to improve stability, increase half life and slow clearance of the protein from blood (see, for example, column 3, lines 38-44). However, there is no teaching or suggestion that introducing RKRRKR into Factor VII would improve stability, increase half life or slow clearance of Factor VII from blood. Thus, because there is no teaching or suggestion that introducing RKRRKR into Factor VII would improve stability, increase half life or slow clearance of the protein from blood, Nicolaisen *et al.* would not have taught, suggested or motivated the skilled artisan to introduce RKRRKR into Factor VII to improve stability, increase half life and slow clearance of the protein from blood.

Furthermore, as disclosed in the specification, introducing RKRRKR into Factor VII allows cells expressing the modified Factor VII to secrete Factor VII in an active form, namely Factor VIIa (page 9, third paragraph). Factor VIIa was known in the art to be less stable than Factor VII- as stated by Nicolaisen *et al.* "Factor VIIa has been found to be a protein susceptible to proteolytic cleavage giving rise to a number of degradation products...." (column 2, lines 28-41) Thus, if the skilled artisan wanted to improve Factor VII stability, increase half life or slow clearance of Factor VII from blood, they would not introduce a proteolytic cleavage sequence

(RKRRKR) that when expressed in cells is an active form, Factor VIIa, that is less stable than Factor VII. The fact that Nicolaisen *et al.* describe modifying a large number of Factor VII residues i.e., 38-39, 32-33, 290-291, 316-316, 341-342, 304-305, 42-43, 44-45, 278-279, 332-333, but fail to teach or suggest modifying amino acids 152 or 153 of Factor VII, let alone introducing a proteolytic cleavage site between amino acids 152 and 153 of Factor VII, is consistent with the position that introducing a proteolytic cleavage site such as RKRRKR into Factor VII would not have improved stability, increased half life or slowed clearance of Factor VII from blood and furthermore, would have had the opposite effect and reduced stability and decreased circulating half life. In view of the foregoing, clearly one skilled in the art would not have been motivated to combine Wolf *et al.* with Nicolaisen *et al.* at the time of the invention.

As a third issue, and the assertion that "one of ordinary skill in the art would have been motivated to combine the teaching to produce a slow release form of Factor VII," as discussed above Wolf *et al.* produces inactive Factor X ("slow release" Factor X) to treat thrombus formation i.e., by inhibiting clotting. Inactive Factor X has a longer circulating half life than active Factor X because inhibitors present in blood, such as anti-thrombin III are able to bind to and inactivate active Factor X, but not inactive Factor X. As discussed above, the specification discloses that introducing RKRRKR into Factor VII enables cells expressing the modified Factor VII to secrete Factor VII in an active form, Factor VIIa, and Factor VIIa has a shorter circulating half life than Factor VII. Thus, in view of the fact that the purported motivation to combine Wolf *et al.* with Nicolaisen *et al.* is "to produce a slow release form of Factor VII," but introducing RKRRKR into Factor VII causes the opposite to occur, namely secretion of an active form, Factor VIIa that has a shorter half life, clearly the skilled artisan would not have been motivated to introduce RKRRKR into Factor VII in order to produce an inactive or "slow release" form of Factor VII. In view of the foregoing, clearly one skilled in the art would not have been motivated to combine Wolf *et al.* with Nicolaisen *et al.* at the time of the invention.

In sum, neither Wolf *et al.* nor Nicolaisen *et al.* provide a motivation to produce claims 1, 2, 13 to 25, 29, 30, 32, 34, 35 and 41. Absent a motivation to combine Wolf *et al.* with Nicolaisen *et al.* at the time of the invention, the rejection is improper and must be withdrawn. Furthermore, in view of the fact that introducing a proteolytic cleavage site into Factor VII so cells express and secrete Factor VII in a form that is less stable and has reduced circulating half life, which is opposite of Nicolaisen *et al.* and Wolf *et al.* clearly one skilled in the art would

have been taught away from introducing RKRRKR into Factor VII. Consequently, claims 1, 2, 13 to 25, 29, 30, 32, 34, 35 and 41 would not have been obvious under 35 U.S.C. §103(a) over Wolf *et al.* (U.S. Patent No. 5,795,863) in view of Nicolaisen *et al.* (U.S. Patent No. 5,580,560) at the time of the invention.

In terms of new claims 64 to 84, neither Wolf *et al.* nor Nicolaisen *et al.* teach or suggest a modified Factor IX, let alone Factor IX modified as in claims 64 to 84. Consequently, as neither Wolf *et al.* nor Nicolaisen *et al.* teach or suggest each and every element of claims 64 to 84, the claims would not have been obvious under 35 U.S.C. §103(a) over Wolf *et al.* (U.S. Patent No. 5,795,863) in view of Nicolaisen *et al.* (U.S. Patent No. 5,580,560) at the time of the invention.

The rejection of claims 1, 24 and 28 under 35 U.S.C. §103(a), as allegedly unpatentable over Wolf *et al.* (U.S. Patent No. 5,795,863) in view of Nicolaisen *et al.* (U.S. Patent No. 5,580,560) and further in view of Amalfitano *et al.* (U.S. Patent No. 6,328,958) is respectfully traversed. The grounds for rejection are set forth in the Office Action, page 6. Namely, neither Wolf *et al.* nor Nicolaisen *et al.* teach using an EF-1-alpha promoter. Allegedly, Amalfitano *et al.* describe a heterologous nucleotide sequence associated with EF1-alpha promoter.

Claims 1, 24 and 28 would not have been obvious in view of Wolf *et al.* (U.S. Patent No. 5,795,863) alone, or in combination with Nicolaisen *et al.* (U.S. Patent No. 5,580,560) or Amalfitano *et al.* (U.S. Patent No. 6,328,958) at the time of the invention. Solely in order to further prosecution of the application, the amended and new claims recite "secreted in an active form." The rejection will therefore be addressed as if applied to the amended and new claims upon entry of this Response.

As discussed above, neither Wolf *et al.* nor Nicolaisen *et al.* provide a motivation to produce a recombinant polynucleotide that encodes a modified Factor VII wherein the modification comprises a proteolytic cleavage site having the sequence RKRRKR. Furthermore, in view of the fact that expression of such a modified Factor VII in cells results in a form of Factor VII (Factor VIIa) that is less stable, clearly one skilled in the art would not have introduced RKRRKR into Factor VII. Likewise, Amalfitano *et al.* fail to provide any motivation to produce a recombinant polynucleotide that encodes a modified Factor VII wherein the

modification comprises a proteolytic cleavage site having the sequence RKRRKR. Consequently, claims 1, 24 and 28 would not have been obvious under 35 U.S.C. §103(a) over Wolf *et al.* in view of Nicolaisen *et al.* and Amalfitano *et al.* at the time of the invention. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) over Wolf *et al.* (U.S. Patent No. 5,795,863), Nicolaisen *et al.* (U.S. Patent No. 5,580,560) and Amalfitano *et al.* (U.S. Patent No. 6,328,958).

In terms of new claims 64 to 84, neither Wolf *et al.*, Nicolaisen *et al.* nor Amalfitano *et al.* teach or suggest a modified Factor IX, let alone Factor IX modified as in claims 64 to 84. Consequently, as neither Wolf *et al.*, Nicolaisen *et al.* nor Amalfitano *et al.* teach or suggest each and every element of claims 64 to 84, the claims would not have been obvious under 35 U.S.C. §103(a) over Wolf *et al.* (U.S. Patent No. 5,795,863), Nicolaisen *et al.* (U.S. Patent No. 5,580,560) and Amalfitano *et al.* (U.S. Patent No. 6,328,958) at the time of the invention.

The rejection of claims 1, 24, 26 and 27 under 35 U.S.C. §103(a), as allegedly unpatentable over Wolf *et al.* (U.S. Patent No. 5,795,863) in view of Nicolaisen *et al.* (U.S. Patent No. 5,580,560) and further in view of Kochanek *et al.* (U.S. Patent No. 5,981,225) is respectfully traversed. The grounds for rejection are set forth in the Office Action, page 7. Namely, neither Wolf *et al.* nor Nicolaisen *et al.* teach using a muscle actin or an MCK promoter. Allegedly, Kochanek *et al.* describe use of the MCK promoter.

Claims 1, 24, 26 and 27 would not have been obvious in view of Wolf *et al.* (U.S. Patent No. 5,795,863) alone, or in combination with Nicolaisen *et al.* (U.S. Patent No. 5,580,560) or Kochanek *et al.* (U.S. Patent No. 5,981,225) at the time of the invention. Solely in order to further prosecution of the application, the amended and new claims recite "secreted in an active form." The rejection will therefore be addressed as if applied to the amended and new claims upon entry of this Response.

As discussed, neither Wolf *et al.* nor Nicolaisen *et al.* provide a motivation to produce a recombinant polynucleotide that encodes a modified Factor VII wherein the modification comprises a proteolytic cleavage site having the sequence RKRRKR. Furthermore, in view of the fact that expressing a recombinant polynucleotide that encodes such a modified Factor VII in cells results in a form of Factor VII (Factor VIIa) that is less stable, which is opposite to the

result desired to be achieved, clearly one skilled in the art would not have introduced RKRRKR into Factor VII. Likewise, Kochanek *et al.* fail to provide any motivation to produce a recombinant polynucleotide that encodes a modified Factor VII wherein the modification comprises a proteolytic cleavage site having the sequence RKRRKR. Consequently, claims 1, 24, 26 and 27 would not have been obvious under 35 U.S.C. §103(a) over Wolf *et al.* in view of Nicolaisen *et al.* and Kochanek *et al.* at the time of the invention. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) over Wolf *et al.* (U.S. Patent No. 5,795,863), Nicolaisen *et al.* (U.S. Patent No. 5,580,560) and Kochanek *et al.* (U.S. Patent No. 5,981,225).

In terms of new claims 64 to 84, neither Wolf *et al.*, Nicolaisen *et al.* nor Kochanek *et al.* teach or suggest a modified Factor IX, let alone Factor IX modified as in claims 64 to 84. Consequently, as neither Wolf *et al.*, Nicolaisen *et al.* nor Kochanek *et al.* teach or suggest each and every element of claims 64 to 84, the claims would not have been obvious under 35 U.S.C. §103(a) over Wolf *et al.* (U.S. Patent No. 5,795,863), Nicolaisen *et al.* (U.S. Patent No. 5,580,560) and Kochanek *et al.* (U.S. Patent No. 5,981,225) at the time of the invention.

The rejection of claims 1 and 29 to 31 under 35 U.S.C. §103(a), as allegedly unpatentable over Wolf *et al.* (U.S. Patent No. 5,795,863) in view of Nicolaisen *et al.* (U.S. Patent No. 5,580,560) and further in view of Kay *et al.* (U.S. Patent No. 5,980,886) is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 7-8. Namely, neither Wolf *et al.* nor Nicolaisen *et al.* teach using a viral vector. Allegedly, adenoviral and retroviral vectors were known in the art for expressing a protein in a liver cell, as exemplified by Kay *et al.*

Claims 1, 24, 26 and 27 would not have been obvious in view of Wolf *et al.* (U.S. Patent No. 5,795,863) alone, or in combination with Nicolaisen *et al.* (U.S. Patent No. 5,580,560) or Kay *et al.* (U.S. Patent No. 5,980,886) at the time of the invention. Solely in order to further prosecution of the application, the amended and new claims recite "secreted in an active form." The rejection will therefore be addressed as if applied to the amended and new claims upon entry of this Response.

As discussed, neither Wolf *et al.* nor Nicolaisen *et al.* provide a motivation to produce a recombinant polynucleotide that encodes a modified Factor VII wherein the modification

comprises a proteolytic cleavage site having the sequence RKRRKR. Furthermore, in view of the fact that expressing a recombinant polynucleotide that encodes such a modified Factor VII in cells results in a form of Factor VII (Factor VIIa) that is less stable, clearly one skilled in the art would not have introduced RKRRKR into Factor VII. Likewise, Kay *et al.* fail to provide any motivation to produce a recombinant polynucleotide that encodes a modified Factor VII wherein the modification comprises a proteolytic cleavage site having the sequence RKRRKR. Consequently, claims 1, 24, 26 and 27 would not have been obvious under 35 U.S.C. §103(a) over Wolf *et al.* in view of Nicolaisen *et al.* and Kay *et al.* at the time of the invention. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a) over Wolf *et al.* (U.S. Patent No. 5,795,863), Nicolaisen *et al.* (U.S. Patent No. 5,580,560) and Kay *et al.* (U.S. Patent No. 5,980,886).

In terms of new claims 64 to 84, neither Wolf *et al.*, Nicolaisen *et al.* nor Kay *et al.* teach or suggest a modified Factor IX, let alone Factor IX modified as in claims 64 to 84. Consequently, as neither Wolf *et al.*, Nicolaisen *et al.* nor Kay *et al.* teach or suggest each and every element of claims 64 to 84, the claims would not have been obvious under 35 U.S.C. §103(a) over Wolf *et al.* (U.S. Patent No. 5,795,863), Nicolaisen *et al.* (U.S. Patent No. 5,580,560) and Kay *et al.* (U.S. Patent No. 5,980,886) at the time of the invention.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 1, 2, 13 to 35, 41 and 64 to 84 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065.

Please charge any fees associated with the submission of this paper to Deposit Account Number 03-3975, Order No. 018743-0278737. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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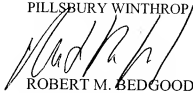

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